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Washington University School of Medicine

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On the Cover:
Wheat causes a significant amount of discomfort to allergy sufferers. Research on "Those Miserable Allergies" is sometimes neglected. See story on page 9.

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Renal Division: Searching for prevention, solving complications

By Sharon Stephens Murphy

There are about 25,000 people in the United States on dialysis. The cost for dialysis is estimated at $350 million and the cost of transplantation is $20-25 thousand per patient.

In 1969 a *Wall Street Journal* article reported, "Only about 1,700 Americans currently receive treatment while an estimated 8,000 people will die this year for lack of it."

The treatment referred to is hemodialysis for victims of kidney disease. At that time nine out of ten victims would die because the process was unavailable to them.

The treatment and research of this disease is relatively new, dating back to the 1940s when hemodialysis was used experimentally. In the 1960s it became more widespread although still not financially feasible for everyone. Since then state and federal funds have guaranteed treatment for those afflicted.

Today, the statistics are staggering. There are about 25,000 people in the United States on dialysis. The cost for dialysis is estimated at $350 million and the cost of transplantation is $20-25 thousand per patient.

Saulo Klahr, M.D., director of the Division of Renal Diseases, stresses that the School of Medicine is involved in research to find ways to treat and improve the quality of life in patients who have the disease as well as to try to find the causes and cures.

"If renal disease continues at the rate we are seeing now," he says, "it is calculated that 50 to 60 out of one million people are going to require dialysis each year. In the United States alone, this would give us more than 10,000 new people every year on dialysis programs."

If this trend is actual, Klahr says the projected cost for the dialytic population for 1980 would be $1 billion.

"Because of the economic considerations, in addition to the fact that the renal patient on dialysis treatment lacks quality of life, we must work to prevent the further rise of kidney disease," Klahr says. "It's an economic as well as a human problem."

Klahr notes a similar situation in the 1940s when the iron lung was developed. "If the scientists had concentrated just in the development and manufacture of iron lungs, we never would have found a polio vaccine. As a result, thousands of people would now be living in iron lungs."

One of the primary known causes of end-stage renal disease is glomerulonephritis. "About 60 to 70 per cent of all the people who require dialysis are patients who have had this disease," says Phillip Hoffsten, M.D., assistant professor of medicine, who is studying glomerulonephritis. "Many times we know this disease exists long before end-stage renal failure occurs.

"Most people are diagnosed while they still have sufficient kidney function to support a normal life," Hoffsten explains. "A person may have glomerulonephritis without it causing any symptoms. Some people live a normal life for years with glomerulonephritis, while others have a much shorter time before renal insufficiency begins. With the advance warning early diagnosis provides, the patient can prepare for the expected outcome of the disease. The object of research in this field is to avert progression of the disease.

"Although people have been studying glomerulonephritis for about 25 years we still know little about the disease," Hoffsten says. "We know it is a very diverse disease, with more than one cause and that at present, medicine does not know how to favorably alter the course of the disease."

Usually the etiologic agent causing glomerulonephritis is not known. There have been cases in Africa in which the organism which produces malaria is the responsible antigen causing nephritis. Also, some patients who have

had syphilis have developed antibodies which are known to lead to glomerulonephritis. "We don't know in a majority of cases what the antigen is but it is a good bet that in many of the cases it may be a virus," Klahr says.

"While we know very little about viral induced glomerulonephritis," Klahr says, "there is strong evidence that this might be one of the mechanisms for the production of nephritis. When there is an antigen (in this case a virus) which causes the production of antibodies, complexes of antigens and antibodies are deposited in the kidneys and produce renal disease. Dr. Hoffsten is trying to understand how this happens and how we can manipulate the resulting renal disease with drugs."

In his research, Hoffsten is infecting mice with a type of virus which causes glomerulonephritis to progress in a predictable way. He and his colleagues are treating and manipulating this progression to try to change the course of the disease. It was during this work that he found that glomerulonephritis is not a hyper-immune state as thought in the past but an immuno-deficient condition.

"We have found that when we inject this virus into the offspring, the mother, who has not received the virus, develops an innocuous infection and becomes immune by exposure to her young," Hoffsten explains.

"Then, we take the mother's spleen and give her offspring those spleen cells which are immune. The babies eliminate the virus and the glomerulonephritis which would normally occur, does not.

"Of course, this is not yet practical for application to humans because it involves the transplantation of cells from one person to another. But at least on a conceptual basis it tells us the real problem with the disease is not hyper-immunity but rather immunodeficiency.

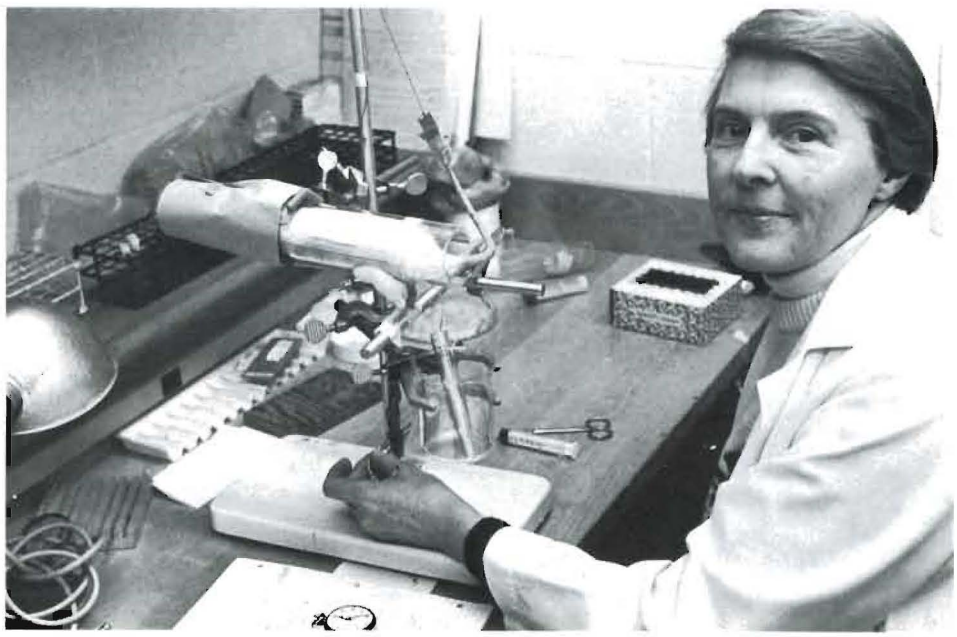
"We are looking at the cells which are responsible for the immunity in the mother's spleen, whether it is a specific kind, a lack of several or a lack of a cooperative effort," Hoffsten says.

"If renal disease continues at the rate we are seeing now, it is calculated that 50 to 60 out of one million people are going to require dialysis each year in the United States alone."

Saulo Klahr, M.D.

"Glomerulonephritis is the most common cause of renal disease in persons younger than age 50."

Phillip Hoffsten, M.D.



"The consequences of untreated obstruction are destruction of kidney tissue reflected by loss of renal function."

Mabel Purkerson, M.D.

"The problem with glomerulonephritis is very much the same problem as with cancer. How does a cancer in you or me continue to progress when normally our immune system should eliminate it? For some reason when we grow a cancer or in this case a virus, our immune system is blinded and does not recognize the foreign growth. When we find an answer to cancer we'll have one for glomerulonephritis too."

Glomerulonephritis is the most common cause of renal disease in persons younger than age 50. Later in the 60s, 70s and 80s arteriosclerosis and hypertension are prevalent causes for renal disease.

Obstructive uropathy also can cause renal disease. Mabel Purkerson, M.D., associate professor of medicine, is concerned with this problem.

"Obstruction to urine flow at some point in the urinary tract occurs frequently," Purkerson says. "Lesions which obstruct the urinary tract have been found in about 3.8 per cent of post-mortem examinations. Figures obtained from autopsies of uremic patients show an incidence of about 25 per cent, including both patients in whom obstructive uropathy was either a contributory or a major factor of renal insufficiency."

Purkerson says the incidence of obstructive uropathy in relation to other causes of renal disease increases in certain age groups, such as infants and children with congenital abnormalities (aberrant vessels, constricting bands) of the urinary tract and elderly males in whom prostatic hypertrophy occurs frequently. Stone formation in the urinary tract may be a cause of obstruction in any age group.

"The consequences of untreated obstruction are destruction of kidney tissue reflected by loss of renal function," Purkerson says. "However, obstruction is generally a remediable cause of kidney failure which requires prompt and accurate diagnosis and appropriate therapeutic maneuvers to preserve and restore renal function."

One specific area Purkerson is studying is the changes in salt and water metabolism observed frequently in patients with obstruction. She and John Buerkert, M.D., assistant professor of medicine at Veterans Hospital, have developed and utilized animal models of obstructive uropathy whereby these changes in salt and water metabolism are reproduced.

"These animal models permit the study of mechanisms which might account for some of the observed phe-

"There are many areas of research because there are a lot of patients who already have advanced renal disease. There is nothing we can do to solve their initial condition. What we want to do is solve some of the complications."

Eduardo Slatopolsky, M.D.

nomena in patients suffering loss of renal function secondary to obstruction," she says. "Better insight concerning the physiological changes occurring with obstruction has opened new and important avenues in our understanding and treatment of patients with urinary tract obstruction."

While some causes of renal failure can be corrected, for those who already have end-stage renal disease, the choices are few: dialysis, transplantation or death. A major area of research at the School of Medicine is to see what can be done to improve the quality of life for the renal patient.

"There are many areas of research because there are a lot of patients who already have advanced renal disease," explains Eduardo Slatopolsky, M.D., professor of medicine. "There is nothing we can do about solving their initial condition. What we want to do is solve some of the complications. Even though the patient can be kept alive with an artificial kidney the renal disease cannot be reversed and it is necessary to try and prevent some of the resulting problems."

W. Ernest Rutherford, M.D., assistant professor of medicine and director of the renal division at City Hospital, Kevin Martin, M.D., research fellow, Slatopolsky and Keith Hruska, M.D., assistant professor of medicine, are involved in three interrelated areas.

One of their areas of research has led to information and answers to the problem of bone disease in patients with renal disease who are maintained on hemodialysis.

Bone disease is a concern in dialysed patients because calcium absorption is a very serious problem for those with renal disease. "Patients with kidney disease do not absorb calcium in the gastrointestinal tract as a well person does," explains Slatopolsky. "We know that one of the reasons calcium is lost in the stools is because of low concentrations of vitamin D in blood." Because vitamin D is first metabolized by the liver and then by the kidney, a person with renal disease is unable to make a metabolite of the vitamin. The result is inability to absorb calcium. "We are changing different factors in the diet, such as calcium, phosphorous, magnesium and are adding new vitamin D metabolites which are still experimental," Slatopolsky says, "to try to correct the problem."

A related complication is the retention of phosphorous. This also causes a decrease of calcium in the blood in direct proportion with the release of parathyroid hormone (PTH). Normally, 70 per cent of phosphorous from the diet should be excreted in the urine. Slatopolsky and his colleagues have been looking for ways to control phosphorous retention which occurs in patients with renal disease. They also have been experimenting with phosphorous binders.

"Phosphorous binders don't taste very good," Dr. Slatopolsky explains. "They leave an after-taste and patients feel nauseated and sometimes vomit. Patients don't like it and it's very difficult to convince them to take it in the dry form. We have been able to make a capsule, but found this greatly reduced its binding potential."

Because the main source of the body's intake of phosphorous is protein, it is impractical to try to restrict phosphorous from a patient's diet. A solution was found by Robert Sparks, professor of chemical engineering and Norbert Mason, senior research asso-

"The average kidney transplant requires two or three days for clearing the PTH build-up."

Keith Hruska, M.D.

ciate in chemical engineering. They developed a new binder which can bind phosphates almost exclusively in the gastrointestinal tract and is active even as a dehydrated gel.

Rutherford and Slatopolsky have tested the gel and have had bread sticks made with it. The bread sticks taste normal and have few side effects. Results have been excellent in patients who eat the bread sticks, with phosphorous under control in a week to ten days.

With phosphorous and vitamin D levels controlled, the deficiency of calcium can be corrected. This is a big step because while the calcium deficiency is very small and difficult to measure, its total effect multiplies over the years a person may have kidney disease. "If you realize a renal patient may have the disease for 20 years and you multiply that small amount even for a period of three years, you are talking about a very large amount of lost calcium," explains Slatopolsky.

As the calcium in the blood decreases, the concentration of calcium drops and this stimulates the parathyroid glands and another complication develops. Parathyroid hormone (PTH) is released to maintain calcium homeostasis. It stimulates the osteoclasts which mobilize calcium from the bone and put it back into the blood.

"This is very good for the blood, but is detrimental for the bones. And over a period of time your bones decalcify and become very fragile and break

"One of the major problems with people on dialysis is that they have accelerated vascular disease."

Herschel Harter, M.D.

easily," Slatopolsky explains.

Keith Hruska is working on a related problem involving how the body handles PTH. Hruska found that the patient with renal disease has a high level of PTH in the blood not only because of increased production but because of decreased destruction.

He found that while the kidney and liver are both responsible for creating fragments of the 1-84 amino acid chain of PTH, the liver only has an uptake mechanism for the intact hormone. Since the kidney handles both the intact hormone and the N-terminal and C-terminal fragments, it is the important organ in the destruction of PTH. As a result the dialyzed patient maintains a high level of PTH.

Hruska is also evaluating the handling of PTH following a transplant. "Renal patients have high levels of PTH but in most cases after a transplant the new kidney is able to clear the buildup of PTH. Levels then remain normal," he says.

Hruska and his associates, Kevin Martin and Jeffrey Freitag, M.D., research fellow, recently have found that the average kidney transplant requires two to three days for clearing the PTH buildup. "We're also studying why some patients continue to have high PTH levels after transplant surgery.

"In another study we're looking at the effect of calcium and magnesium on PTH action. We know levels of calcium will determine PTH release," Hruska explains, "but we think calcium may also play a role in the actions and degradation of PTH."

A method to measure PTH in the blood developed by Slatopolsky brought world fame to both the Division and Slatopolsky. He immunized a rooster with PTH about eight years ago and it developed a very sensitive antibody which enabled the measuring of PTH in picograms. Although the rooster is dead now, it left behind enough antibody to supply the Division for a long time. While the rooster was alive, the renal division supplied laboratories all over the world with the valuable antibody.

Also working on complications of renal disease is Herschel Harter, M.D.,

assistant professor of medicine and medical director of the Chromalloy American Kidney Center.

"One of the major problems with people on dialysis is that they have accelerated vascular disease," Harter says. "Their atherosclerotic vascular disease accelerates at a rate faster than a diabetic. If patients are to survive for prolonged periods of time, we must find the cause for this metabolic condition."

More than 80 per cent of the patients maintained on hemodialysis have diabetic tendencies, Harter says. To evaluate the etiologies of this diabetic state, Harter in conjunction with Irene Karl, Ph.D., of the Division of Metabolism, has been using the epitrochlaris muscle of rats. Karl and David Kipnis, M.D., head of the Department of Medicine, have studied this muscle in normal and diabetic mice. They found that in diabetic rats there is an accelerated rate of amino acid release. This protein breakdown is not necessarily related to the glucose that is being taken up by the muscle.

Harter and Karl used uremic rat models, and fed them low, medium and high protein diets. After ten days on the respective diets the muscles were removed and incubated for one or three hours to determine their metabolic function. "We found that the uremic muscle also had an increased release of amino acids similar to the diabetic muscle, although less severe," Harter says. "However, while muscles from diabetic animals have a decreased glucose uptake, the muscles from uremic animals have an increased uptake. There are several possibilities for this finding, which we are currently evaluating.

"Our object was to improve the metabolic function of the muscle. We found that when we fed the rats a low protein diet the muscle was more normal. On the other hand, the muscles from animals fed a high protein diet were very abnormal. Thus it appears that diet alone may affect these parameters. It also appears that increased glucose uptake and accelerated amino acid release may not be related to the same metabolic defect. There may be different metabolic aberrations affecting each of the observed abnormalities."

Harter and his colleagues are studying several different aspects of the apparent diabetic tendencies of dialyzed patients by utilizing the rat model, altering both diet and hormonal imbalances and thus hoping to correct the defects. "Once we correct the diabetic state we can expect to protect the patient from vascular disease for a longer period of time," Harter says.

Another complication affecting renal patients is an increased incidence of gastrointestinal disease. "It used to be thought that a high percentage of dialyzed patients had ulcers," Harter says. "To examine this possibility we evaluated 100 patients using gastrointestinal X-rays, endoscopy and biopsy of the stomach and duodenum in conjunction with David Margolis of the Department of Gastroenterology. We found a very high incidence of gastritis. Approximately 40 per cent of our patients, most of whom were asymptomatic, had some degree of gastritis and that was confirmed by biopsies," he says. "No ulcers were documented. We took the most severe cases and treated them with a calcium carbonate preparation.

Fifty per cent of the patients improved. Thus it appears that gastritis and duodenitis is an extremely frequent complication of uremia which may be benefited by conventional medical management. We plan to study transplanted patients next."

Another current study is underway in which the researchers are studying hormones in chronically dialyzed patients. "No studies have been well performed on the responses of epinephrine and norepinephrine in chronically dialyzed patients," Harter says. "These two hormones assist in the control of your blood pressure. We will study the clearance of norepinephrine by the artificial kidney in nonhypertensive and hypertensive dialysis patients. We will also document their respective responses to position, medications and known stimuli of norepinephrine release. We also plan to evaluate the responses to medications and stimuli in patients with severe renal disease who are not yet on dialysis."

This, as well as other research in the Renal Division, is designed to improve the quality of life for the patient with severe renal disease. Harter and his associates recently had the opportunity to evaluate a new device which, in the near future, may greatly improve the quality of dialysis and mobility of the renal patients.

Called the Wearable Artificial Kidney (WAK), the device was developed by Dr. Willem Kolph, of the University of Utah, who was also the first person to develop dialysis. With the assistance of Carol Weerts, coordinator of the dialysis unit. Harter evaluated the WAK and made recommendations for improvements.

"The WAK is compact, lightweight and wearable. However, the machine is 30 per cent less efficient than a regular dialysis machine and still must use a dialysate bath, making it cumbersome. Newer sorbents will improve its efficacy."

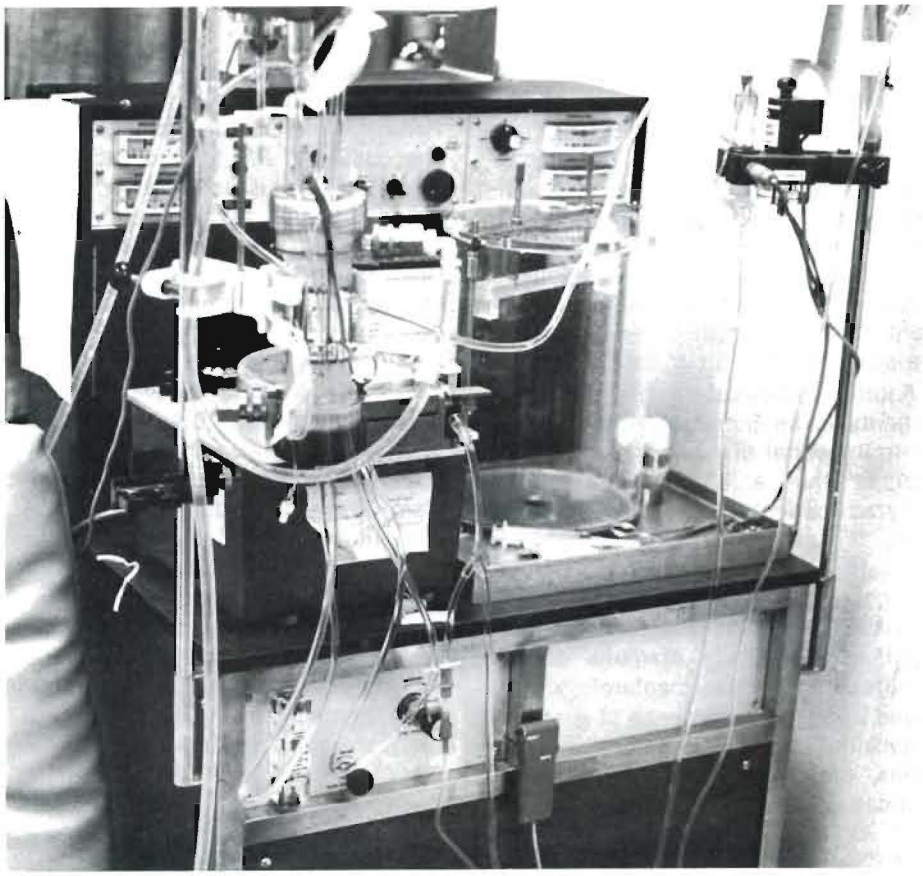
One of the advantages of the machine is that a person with an office job could dialyze at work with the portable unit, leaving more free time for the patient and his family. The other advantage is that a renal patient could travel with much less difficulty using the portable unit.

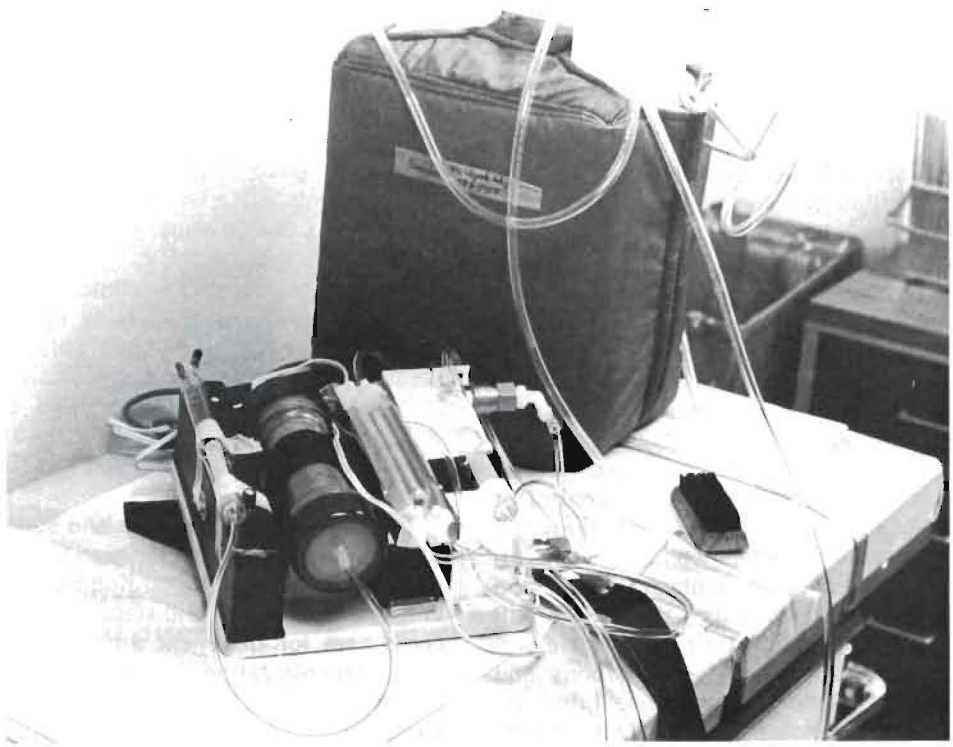
"We are going to recommend some improvements," Harter says, "and if these things can be done, I think it will be a very good product."

While research, both clinical and basic, is a major responsibility of the Division, it isn't the only one. It also is involved in teaching and patient care.

Postdoctoral fellows are trained by the Division and 24 senior medical students each year rotate through the Division.

The Division also operates and staffs the W.U. Chromalloy Kidney Center which includes the six-bed Kuhn-Pelton unit. Patients with end-stage disease come here for treatment and dialysis, or for transplantation. Renal housestaff are responsible for hospital patients with kidney problems and renal division





"The goals of renal disease research are to prevent future generations from the threat of renal disease and to improve the quality of life for those who have no other choice than dialysis."

Saulo Klahr, M.D.

specialists serve as consultants to other physicians.

Renal disease has many facets and most researchers agree that the complete cure for it is many years away. As in most research, one of the major factors is adequate funding. Although the cost for dialytic population will cost $1 billion in a few years, renal research still isn't a priority.

"In the past fifteen years it has come a long way," Klahr says. "We used to be concerned only with treating end-stage renal disease. Efforts began in 1960 to develop better and more effective ways of dialysis and transplantation. In the '60s, great strides were made in transplantation, but there has been little change in this decade.

"The emphasis now," Klahr says, "is on the prevention of the disease, as well as solutions to some of the complications which weren't evident before. The goals of renal disease research are to prevent future generations from the threat of renal disease and to improve the quality of life for those who have no other choice than dialysis."

The regular dialysis machine (above) compared to the recently developed Wearable Artificial Kidney WAK (below). While the WAK is 30 per cent less efficient it does provide greater mobility.

Those miserable allergies: new interest in a common illness

By Glenda King Rosenthal

Approximately 10 per cent of the American population, including children and adults, is affected by it. Of all the chronic illnesses, it is the number one cause of absenteeism in schools. Many millions of dollars in loss of manpower are caused by it every year. At Washington University's own Medical Care Group, more than four per cent of the patients are treated for it.

The problem may not be fatal, but allergic disease can be a debilitating, confining illness, and also can be financially important, when viewed over a lifetime.

Timothy J. Sullivan, M.D., assistant professor of medicine and director of the Adult Allergy Clinic at the School of Medicine, says, "A little mathematics makes the problem obvious. There are some 220 million people in the United States and at least 10 per cent of them have an active allergic disease. The problem is there are fewer than 2,000 allergists in this country to treat illnesses which affect more than two million people. That's a rather alarming ratio."

Fewer than half the medical schools in this country have someone on the faculty who spend their full-time investigating and caring for patients with allergic diseases. "Consequently," Sullivan says, "a large number of physicians graduate from medical school with no more than a cursory knowledge of the immune system and diseases resulting from immune inflammation.

"I must admit I was brought up on rather traditional grounds medically. I was educated in a medical school which didn't have anyone on the faculty who treated allergic or immune diseases. We used hospitalized patients almost exclusively as our examples of important illnesses," Sullivan says. "The allergic diseases, with the exceptions of very severe asthma, shock reactions or anaphylaxis, simply aren't seen in the hospital. It's rare that the allergy patient being treated for his illness ever needs hospitalization."

Sullivan says most medical students are educated to believe that if an illness isn't potentially fatal, it's a trivial one. If it's chronic and mild, as most allergic diseases are, it is considered to be vastly less important than an acute, disruptive illness of short duration.

"I think because of these rather practical factors, medical students, myself included, simply have not been made aware of how prevalent these illnesses are and how economically important they are if nothing else."

Rheumatologists have to take care of some immune illnesses, Sullivan says, because a high proportion of rheumatic diseases are caused by immune mechanisms. "There is an overlap. But, nevertheless, rheumatologists really have little interest in the large subset of immune illnesses which manifest themselves as allergies, such as asthma, hayfever, hives or anaphylaxis.

"Unfortunately, this aspect of medicine really doesn't generate much interest in medical schools," he says, "It usually isn't until a physician gets out into practice that he is confronted with the need to evaluate and treat allergic illnesses. Naturally, it's hard to get excited about an illness you have never seen.

"As a student, asthma was something you thought you could quickly come to grips with by opening a book and reading about the proper treatment," Sullivan says. "I didn't regard hayfever or urticaria as significant illnesses while I was in medical school. It's not like bleeding from an ulcer. But when we look at it on a larger scale, spread out over a lifetime, it's deserving of some attention. But it is that kind of thinking, which I certainly typified, that's given us the situation which exists today. We have too few specialists for too many patients, with too little understanding of the processes involved."

The development of approaches to the treatment of allergies has almost exclusively been dependent upon previous trial and error, because there was virtually no understanding of why a treatment was working. A prime example is the use of allergen injections to desensitize allergy patients. As early as 1910 physicians had empirically discovered a way of giving injections of allergens to reduce the severity of allergies.

"In the late 1800's, German physicians began to make anti-sera against everything they could isolate," Sullivan says. "The first large success was in the treatment of diphtheria. Horse anti-serum was developed against the diphtheria toxin. It could prevent the appearance of lethal aspects of the disease, or it could stop them once under-

way. Consequently, a lot of enthusiasm was generated for developing anti-sera against practically everything."

However, it soon became clear that injecting horse serum into a person might cure the illness, but a wide variety of new problems would develop. "Soon people became allergic to horse serum," Sullivan says. "An attempt was then made to immunize people themselves, a much more efficient approach. It was that kind of thinking—either giving an immune serum or causing patients to make their own—which prompted physicians in the late 1800's to believe they could prevent virtually any illness through immunization."

In this milieu physicians began injecting extracts of pollens, mold spores, dust and other materials into allergic people in an attempt to immunize and thereby protect them. "We now know the improvement which occurred had little to do with immunizing a patient against pollen," Sullivan says. "The mechanism by which it acted was quite different from the antibody production physicians intended to activate. Yet, the upshot was that it worked. Because it didn't work for all people, however, there was an incentive to keep looking."

A variety of medications for the treatment of allergies were subsequently discovered, again by trial and error. German physicians extracted adrenal glands and found that in them was a substance which had several striking pharmacologic properties. "They called it adrenalin," Sullivan says. "It was quickly found that adrenalin could reverse many types of allergic reactions. By the turn of the century, physicians were administering adrenalin to people with asthma and a variety of other allergic reactions. Again, the mechanism was not understood, but it didn't make a lot of difference at a time when no other drugs were available. It worked nicely."

Theophylline is another example of a chance finding for the treatment of asthma. "To this day I am unable to determine why physicians first tried

Mast cells: where histamine is produced and stored.

theophylline for asthma treatment," Sullivan says. "It was one of a family of drugs isolated from tea and coffee and then synthesized by the chemists; it was simply tried and it worked.

"The upshot of this is the major drugs we use to treat allergic diseases were developed empirically. Injection, adrenalin and theophylline therapy were well underway by the mid-1930's. All of this was accomplished without the slightest idea—although plenty of theories existed—of how it worked."

According to Sullivan, the next major addition to the treatment of allergic diseases came with the development of antihistamines around the time of World War II. Histamine was recognized as an important mediator of allergy as early as 1910, and in 1937 French chemists succeeded in designing drugs to block histamine actions.

"An understanding of one aspect of the problem led to a specific, effective treatment," Sullivan says. "Our incomplete understanding of other fundamental processes in allergy has severely limited the development of more specific cures. Steroid hormones introduced in the 1950's and now cromolyn sodium are again being applied to allergic diseases with some success."

Sullivan feels this empirically arrived at treatment works fairly well in the management of most allergic diseases. "However," he says, "there are some treatment failures, many times despite expensive, long, drawn-out treatment. So, from the point of view of just treatment alone, we're in a quandary. We have some effective medications, but we only partially understand how they work. I view this as a rather large, significant problem in approaching the remaining therapeutic impasses.

"We can handle most of our allergy patients but there are a good number of patients who are still refractory and are only partially helped by injection therapy or desensitization. Our empirically arrived at tools have carried us a long way, but we clearly need deliberately developed medications and interventions."

According to Sullivan, the National Institutes of Health are trying to encourage and support the development of academic people who study, investigate, and teach the care of immune diseases. In conjunction with this idea, Sullivan is the recent recipient of an Allergic Diseases Academic Award.

"The NIH and the Department of HEW have begun to put a greater emphasis on this very neglected area in clinical medicine," Sullivan says. "One of the devices they're using to encourage the clinical investigation and clinical teaching of immune diseases is to specifically allocate financial support for the development of academic allergy people."

Sullivan feels there is definitely an educational gap in the study of allergic diseases. "The award should bridge several gaps, primarily that of developing investigators and educators," he says. "That's really the stated purpose, but there is an even more important one. That is to provide each institution with an academician and educator in allergic diseases. What's happening on an overall scale is we're attempting to get medical educators and investigators in places where they can acquaint medical students with the proper evaluation and care of patients with allergic diseases. We also want them to know enough to be able to recognize when the patient needs help from a specialist, even though the majority of these patients can be cared for by any

physician with a basic understanding of the principles involved."

There has been an overwhelming increase in the understanding of the immune system over the past fifteen years. According to Sullivan, there is a great deal now known about the fundamental mechanisms by which immune diseases occur, and specifically a great deal is being learned about the allergic diseases. This opportunity to apply rapidly accumulating basic information to clinical problems is another important reason why the NIH is now encouraging investigators to devote their clinical and research attention to the immune system.

Another reason is the new, effective, but potentially dangerous medications used for some patients. "Use of many of these drugs requires a great deal of familiarity which most physicians don't as yet have," Sullivan says.

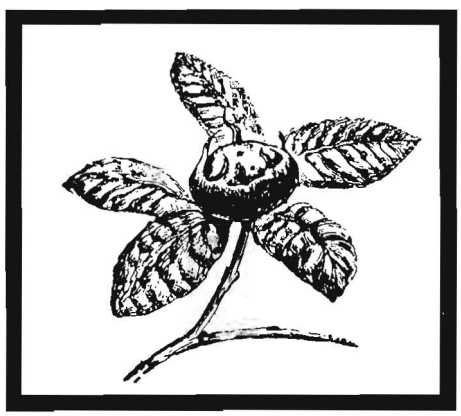
A unique knowledge of immune illness is also necessary in effective injection therapy. Sullivan feels this has to be regarded as potentially lethal intervention. "We're giving the patients substances to which they are extremely sensitive, and if it isn't done properly, it could prove fatal. The improper use of these materials killed a child this year in East St. Louis. It is not a casual undertaking," he says.

The NIH is also encouraging a skilled knowledge of injection therapy. This type of therapy can be expensive in time, as well as money. "Some allergy patients require weekly or biweekly injections for a year and then monthly injections for another couple of years," Sullivan says. "That's the only way of intervening in an allergic illness when the pharmacologic agents we currently use fail."

The cost of this therapy precludes a lot of people from eagerly seeking care for allergy problems. Even though it's spread out over a long period of time, Sullivan says that in this community an evaluation can cost anywhere from $125-$300 depending on the nature of the illness and how many X-rays are necessary. "This cost isn't too different from an internist's work-up on someone with liver or kidney disease. The difference is it is not likely to be a fatal illness. It is an avoidable expense."

People are more likely to seek help for their children than they are for themselves. "Asthma in children is much easier to treat when the disease is of recent onset. But the point is, a lot of people feel obstructed from seeking care for an allergic disease because they can live with it and have other pressing demands on their resources."

Sullivan hopes the recognized need for specialized allergy care will influence insurance companies to pay for outpatient treatment. "More and more insurance companies are willing to pay for outpatient care. There will be more funding available for the general physician to take care of allergy problems, if they know how. There also will be more people seeking care on a private basis from allergy specialists."



Sullivan hopes that through his NIH-sponsored research a better understanding of the immune system will develop, along with a more rapid, effective and efficient way of clinically treating allergy patients.

"We now know, for example, that a unique IgE antibody is responsible for allergic reactions," he says. "This antibody appeared late in the development of animals, and it's found only in mammals. The important point is this just isn't a residual part of the immune system. It's something that deliberately evolved, and in the past two years it's become clear why."

According to Sullivan, the IgE antibody appears to be a protective device against parasites. As a general rule, people in tropical countries don't have hayfever or asthma, but they do have parasites.

"One British study showed that children coming from tropical countries to Britain had virtually no asthma or hayfever," Sullivan says. "But within five years of their arrival, they had the same percentage of hayfever and asthma as the British children."

There are many reasons why that could be, but the prevailing attitude, according to Sullivan, is that their immune system, which was previously involved in the protection against parasitic infection, became idle. "Their immune system began to focus on environmental factors it had no business focusing on.

"It's believed that the more industrialized we become, the more likely our immune system will attack environmental invaders such as dust, pollens, mold spores and animal danders. So, the allergic illnesses appear to be a spectrum of illnesses that are in part a direct result of improving our lives," Sullivan says.

Sullivan became interested in exactly what happens during an allergic reaction, because he felt a thorough understanding would permit researchers to modulate the reaction at will. "The specificity of the allergic reaction comes from the production of these IgE antibodies, which are ordinarily produced when we're invaded by parasites. This antibody doesn't circulate in the blood and attack antigens the way other antibodies do. It does circulate, but in very small quantities. On the other hand, it becomes bound to tissue cells which are called mast cells."

The mast cells are virtually the only place in the body where histamine is produced and stored. "Let's take the example of people allergic to ragweed pollen. When they breathe it in, pollen hits their eyes, nose, airways and skin and pollen proteins begin to diffuse through the tissues.

Timothy J. Sullivan, M.D., hopes to gain new insights into the workings of the immune system through laboratory research.

"The person who is allergic to these substances has already made specific IgE antibodies after previous exposures and has coated the surface of the mast cells. When the ragweed proteins encounter IgE on the mast cells, a reaction occurs which activates the mast cell interior," Sullivan says. "This causes the cell to release many kinds of molecules, histamine being the one that is best understood."

According to Sullivan, there are enormous quantities of histamine in these cells. "There isn't a tissue in the body, except perhaps the brain, that normally isn't partially regulated by the mast cells in the tissues. This biological concept developed in very primitive animals. The biologic idea of making the secretion severe and specific enough to stop invading parasites came later.

"The crux of our studies on mast cells," Sullivan says, "is that by studying the isolated cell we hope to be able to ferret out which of the pharmacologic actions that we know to occur in complex tissues can be attributed to effects on the cell and which are due to alterations in environment. Our objective is simple: the more perfect regulation of mast cell function in the allergic situation."

Sullivan hopes that in the future this dimension of the immune response will be effectively controlled. Until recently, drugs to treat the allergic diseases have been accidentally discovered. "We're just beginning to systematically work out the mechanisms of actions of the drugs which are currently used. We have to understand the mast cell function to pharmacologically regulate that function when the diseases are apparent. It's been impossible so far to prevent the formation of IgE antibodies."

Attempts have been made to understand what portion of the IGE molecule binds to the surface of the mast cell. "As soon as we understand that, we'll attempt to manufacture molecules which resemble portions of the IgE molecule. This should in turn prevent binding to the mast cell," Sullivan says. "If we can do that, we can block

all of the IgE mediated events because it has to be attached to the surface of the cell to deliver its signals."

Current injection therapy apparently doesn't significantly affect the formation of IgE molecules, even though the patient might be markedly better. According to Sullivan, it appears that the mechanism by which these injections work is a combination of many things. "The major factor seems to be in preventing the mast cells from producing these abrupt secretions which cause symptoms. The body can cope with small amounts of these mediator molecules. It's the abrupt, explosive release of histamine that causes a clinically apparent allergic reaction, such as an allergic reaction to penicillin.

"For example, if you were to hold in your hand the amount of ragweed pollen that hits you each year, you could barely see it," Sullivan says. "Yet that tiny amount of pollen provokes intense symptoms."

However, over a period of six to nine months, a patient's tolerance can be built up to the point of desensitization. "We can markedly change the patient's degree of sensitivity," Sullivan says. "The question is, have we reduced their sensitivity to a level at which they don't clinically react. We can build up the degree of tolerance in everybody; we can reduce the clinical symptoms in 8 out of 10 people."

The ideal would be to develop a level of tolerance in the allergy patient so their clinical symptoms would be nonexistent. Or, if the symptoms were there, they could be easily suppressed. "Currently it takes a long time for desensitization therapy," Sullivan explains, "and there are those 15 out of 100 patients who don't respond. This type of therapy isn't a cure; it is a negative modulation which then makes the drugs more satisfactory. We're now investigating why the cell turns off when it is gradually presented with increasing quantities of an allergenic substance."

Sullivan hopes that by biochemically understanding how a cell is activated, it will permit researchers to ask how the cell becomes deactivated. "These processes cannot be separated or solved independent of each other. We are now able to investigate how the gradual presentation of antigen turns the cell off. Hopefully by understanding that process we can come to grips with a more rapid, effective and efficient way of dealing with people."

At the present time, none of the clinically important allergic diseases can routinely be cured. Most can be easily suppressed with avoidance measures or medications which don't make people ill. However, Sullivan points out there is still that 1 in 100 patients who doesn't obtain adequate relief from any of the current methods.

Sullivan emphasizes that one generally measures research in terms of years, not weeks or even months. "We are trying to follow a systematic line of investigation. The price one pays for that," he says, "is research progress appears relatively slow, even though it is definite and thorough."

In the next five years, Sullivan hopes to have a fairly good understanding of the major control mechanisms which regulate mast cell function. "Through our research we may generate the deliberate development of a whole new family of medications, as opposed to the chance findings we've had in the past. What's certain is that we'll know quite a bit more about how the mast cells are regulated, and in turn how to purposely regulate them."

Sullivan became interested in studying the immune system while on a tour of duty with the Special Forces in Vietnam. "I realized that many tropical and parasitic illnesses are a result of immune attacks on infectious organisms and/or the failure of protective immunity. I became interested in the immune system by living among people with a spectrum of illnesses I had never seen before. One could see the destructive and the protective aspects of the immune system. We usually don't see the immune system in such obvious activity. In a tropical country where sanitation is poor, one constantly sees people battling against environ-

mental problems and infectious processes. One quickly realizes how important immunization is when you see these problems in action. The immune system became very real to me, and this only emphasized how little we understand it."

Sullivan found that a disease such as malaria is a satisfying one to treat because the patient feels so much better in a short time. "Because I was in the same location for thirteen months, I often treated the same patients for malaria four or five times. It's extremely satisfying to take care of people, but one has to balance long-range gratification against immediate gratification. That's the difference between treating a disease and solving it."

Sullivan feels he has to balance what he thinks his effectiveness can be as an educator and investigator against a possible role as a full-time clinician. "I hope I can teach enough about my chosen area to developing physicians so they can go out, amplify that knowledge, and apply it. Secondly, I hope to be lucky enough and smart enough to improve the way immune diseases are treated. I find it extremely rewarding to be tackling problems, solving some of them, and participating in the evolution of medical knowledge.

"Very seldom will someone have a dramatic breakthrough in the laboratory that's going to help millions of people. One can't be so grandiose as to expect that will happen," he says. "But laboratory research on the immune system can add a great deal clinically. We now know so little about the human immune system; there are many gains to be made in the field. I hope to be able to translate some of these laboratory phenomena into clinical changes. It's my hope that I'm going to be effective enough as an investigator and educator that my time here will have considerably more impact than what I might have accomplished treating patients with our current insights."

Harvest time is particularly difficult for the allergy sufferer.

War on food additives continues

By Linda Nielsen Weller

Each year food processors add more than 200,000 tons of monosodium glutamate (MSG) to foods in largely unregulated amounts. Yet, MSG is known to have toxic effects on experimental animals, especially immature animals.

In light of this, a scientific advisory committee recommended in November that MSG, along with hydrolyzed vegetable protein (HVP), be banned by the FDA in infant and junior foods.

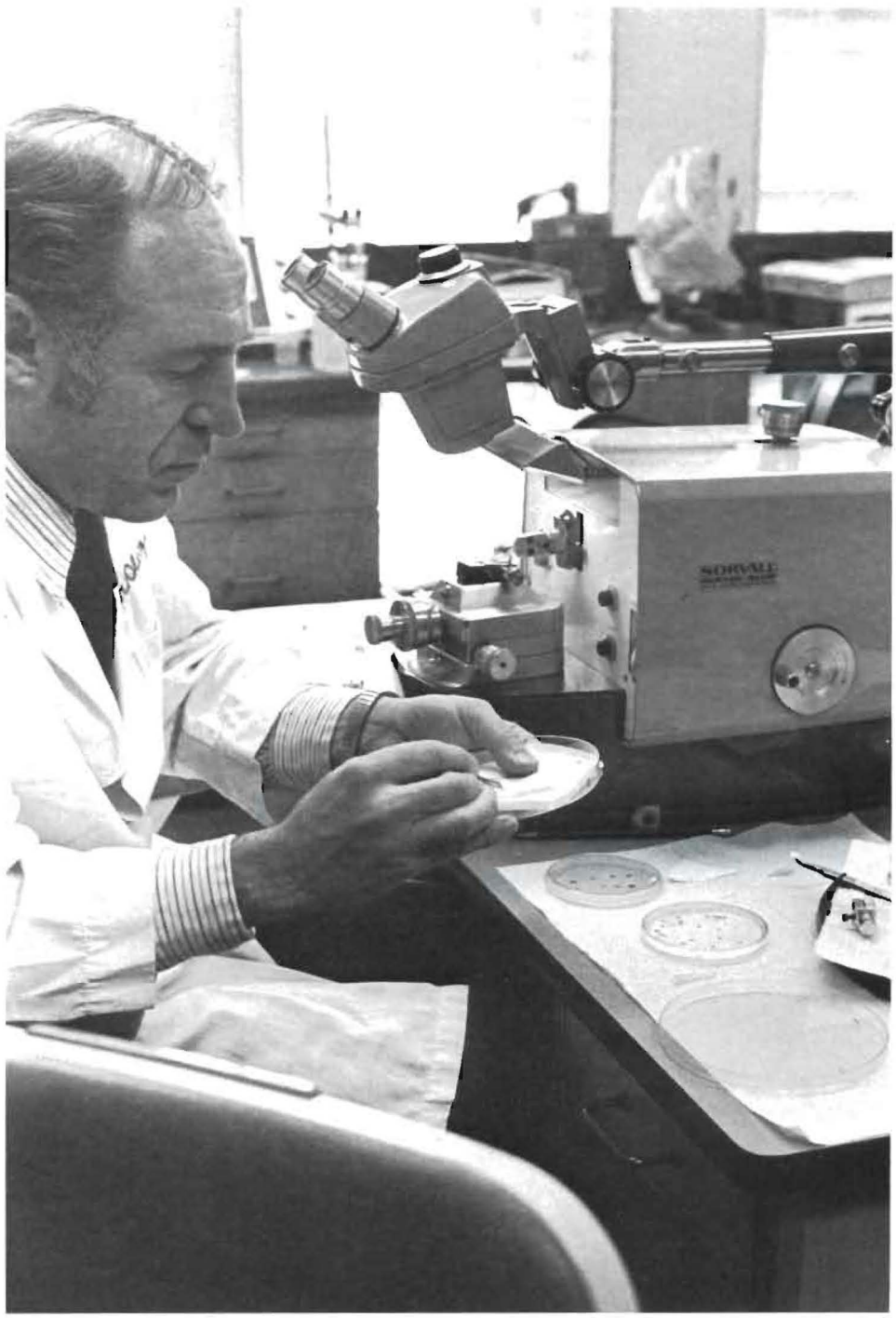
Strongly supporting this measure is John W. Olney, M.D., associate professor of psychiatry and neuropathology, who has supported a ban since 1969. His research has shown that MSG causes brain damage when administered by mouth to young animals.

The Advisory Committee's recommendation that MSG and HVP be banned received little notice. For one reason, the additive HVP is not well-known and secondly, most people believe MSG was taken out of baby foods years ago.

Olney says the latter is a misconception. "MSG really was not taken out of infant and junior foods and an official ban is the only appropriate way to deal with the problem."

Olney reported new findings in November at the annual meeting of the Society for Neurosciences in Toronto. Theodore J. Cicero, Ph.D., associate professor of psychiatry and neurobiology, also attended. They said even when MSG is administered to animals in doses lower than those required to cause brain damage, it resulted in elevated blood levels of two hormones. Testosterone, the male sex hormone is one of the hormones affected. The other, luteinizing hormone (LH), is a pituitary hormone which is transported in blood to the testicle where it stimulates output of testosterone.

Olney and Cicero say the basis for these hormonal changes is that MSG



is able to stimulate certain brain cells. It is by stimulating these cells, the researchers believe, that MSG causes sudden changes in hormonal levels.

"We cannot say yet whether the effects of MSG on hormonal systems will give further basis for questioning the widespread use of the additive in foods," Olney says. "Many more studies will have to be undertaken. In these studies it will be important to ascertain further the effects of daily MSG intake on the immature organism. We suspect that even at relatively low doses, it might cause subtle but repetitive disturbances in certain hormonal systems which are important for normal growth and development."

The November recommendation came from a scientific committee of the Federation of American Societies for Experimental Biology (FASEB). The committee was asked in 1973 to study MSG and HVP by the Commissioner of FDA who was under pressure at the time from the Senate Nutrition Committee.

What do the FASEB recommendations mean to the consumer? "It is too early to tell," Olney says, "but the MSG and food industries probably will wage new offensives to delay or obstruct regulatory action. The FDA has indicated they will hold formal hearings to give interested parties ample time to file complaints against the FASEB recommendation.

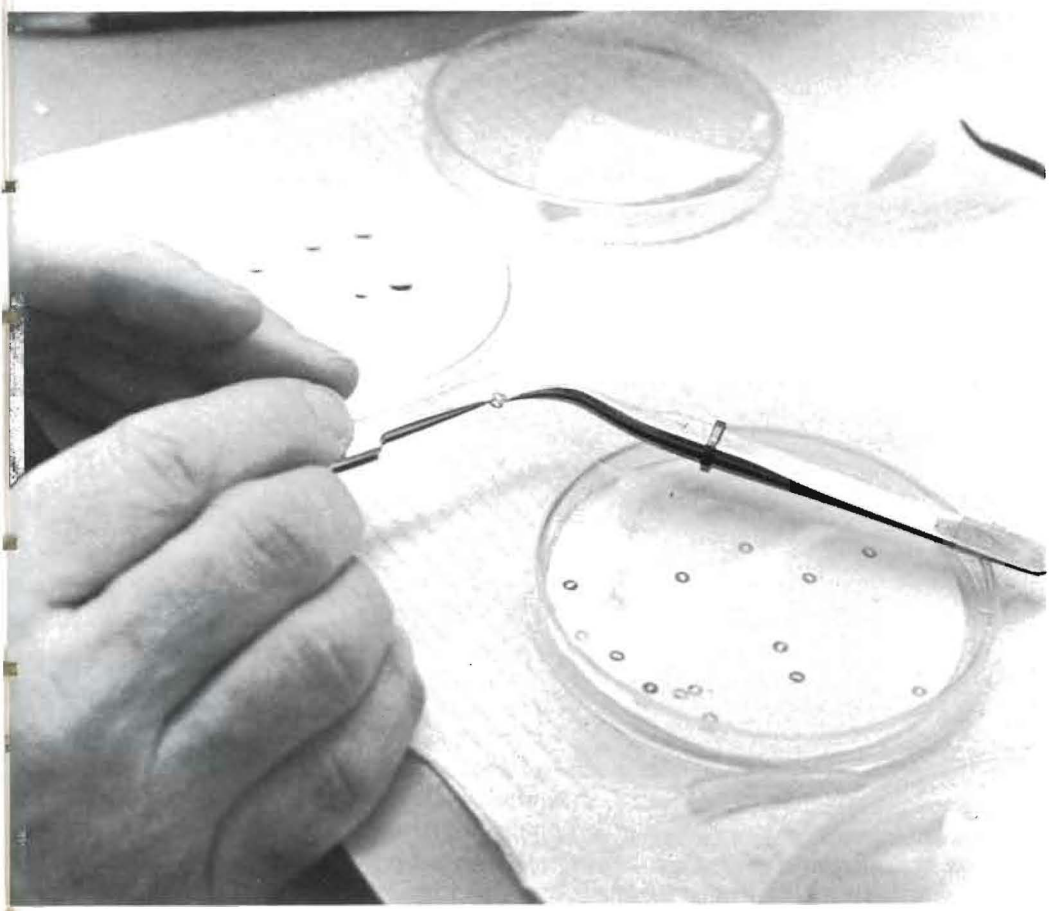
"It will be interesting," Olney says, "to see what action, if any, the FDA finally takes. This is a tough regulatory problem. The FDA is under tremendous pressure from the MSG and food industries to avoid placing a ban on the use of MSG in baby foods. Such action would represent official recognition that MSG poses a significant hazard to at least one large segment of the population, the immature human."

Banning the substances in baby and junior foods is only one part of the picture. "Young people, including infants and young children, actually eat many foods not specifically designated as infant or junior foods," Olney explains. "A ban on MSG in infant and junior foods does not actually protect these young people from MSG intake.

"Food processors in this country and around the world add thousands of tons of MSG to foods each year. Once the FDA acknowledges that MSG poses a hazard to young people, the only way this sensitive population can truly be protected against the hazard is to ban all use of the additive. An alternate, but somewhat less effective approach, would be to require a label warning that food containing MSG is hazardous for the young. Obviously neither approach is acceptable to the industries concerned," Olney says.

According to Olney, baby food manufacturers have used MSG as a flavoring additive since the late 1940s. In 1969 it was brought out in Senate Nutrition Hearings that infants have no taste for MSG. It had been added solely for the mothers' benefit. Later that year the industry, while denying that MSG posed a hazard to the developing brain, announced they would voluntarily stop using MSG in baby foods.

"This move had its intended effect," Olney says. "The public equated it with an official ban and developed a secure feeling that their infants and children were being maximally protected. The facts are, however, that MSG still is being added to the foods that infants and children eat and the FDA never has acknowledged that MSG is hazardous to infants or to anyone else.



In his study of the effects of MSG and other additives on small animals, John W. Olney, M.D., utilizes the ultra-microtome (far left). The device cuts the brain tissue into minute sections. He then mounts the pieces of tissue on tiny copper grids (this page), and views them under a microscope in order to determine if brain damage has occurred

"In 1970, the FDA referred the issue to an industry-dominated panel of food specialists. Their failure to question the safety of MSG gave FDA the necessary backing to continue listing MSG as 'generally regarded as safe (GRAS),' " explains Olney.

"I cooperated fully with the panel," he says, "and I was very disappointed when they wrote a pro-industry report. I later learned that the chairman of the panel had direct financial ties with both the MSG and baby food industries. In addition, most of the other panel members were employed by or otherwise financially dependent upon the food industry, which paid thousands of dollars in 1970 to support the panel's operations."

As a witness at Senate Nutrition Hearings in 1972, Olney testified that the 1970 Advisory Panel on MSG was riddled with conflicts of interest. He noted panel members apparently had been chosen for their industry loyalties rather than scientific qualifications and the panel demonstrated extreme biases in dealing with the MSG issue.

He says he recommended that MSG and all other questionable GRAS additives be re-evaluated by a new committee of truly qualified, independent and objective scientists. It was this committee which recently unequivocally recommended that the FDA place an official ban on the use of MSG in baby and junior foods.

The other substance, HVP (hydrolyzed vegetable protein) is relatively unknown to most consumers. HVP is a product of hydrolysis, a method of breaking down proteins into amino acids such as MSG. Most HVP preparations are rich in MSG and also contain related molecules which act in concert with MSG to increase its brain damaging potential, Olney says.

"Methods for preparing HVP from proteins vary; some methods involve removal of other ingredients to leave almost pure MSG.

"The baby food industry began adding HVP to flavor infant foods at the same time they agreed to stop adding MSG," he says.

Olney reported his research on hy-

The powerful electron microscope is a key instrument in examining and photographing brain tissue under study. The device enables Olney to detect the extent of brain damage cells in animals that have been fed food additives.

drolyzed proteins two years ago in the "New England Journal of Medicine." These findings played an important part in the conclusion of the FASEB committee this month that HVP also should be banned from use in baby foods.

"I don't know why the industry is so intent upon fueling consumer advocate fires," Olney says, "but any way you look it it, they only pretended to stop adding MSG in 1970 and, in fact, have been adding it all along."

When asked how much MSG has been added under the HVP label, Olney says: "I have no idea. Confront FDA with this question and they refer you to food industry representatives who do not seem to know themselves. Since the apparent aim in using HVP is to get enough MSG into the food to give it flavor, they probably have been introducing substantial concentrations of MSG.

"In any event, the FASEB committee would not have asked the FDA to ban the practice if they did not consider it potentially detrimental to the health of infant and junior consumers."

While the FDA is deciding whether to place a partial ban, full ban, or no ban on MSG and HVP, Olney and his research colleagues at the School of Medicine intend to continue exploring the effects of MSG and related compounds on immature brain and hormonal systems.

"These compounds are of extreme interest to the neuroscientist," Olney says, "because they excite nerve cells. I started studying MSG back in 1967 because of this intriguing effect on nerve cells, and it was largely by accident that I discovered its brain damaging potential."

In the upcoming months, FDA hearings will determine what, if any, limitations will be placed on the use of MSG and HVP in baby and junior foods. If the two substances are banned from these foods, it is conceivable that further restrictions might be forthcoming to protect children as they consume foods not designated specifically for babies or juniors.

Similar to the electron microscope is the leitz microscope which Olney also utilizes to view and to photograph damaged brain tissue. This smaller microscope operates at lower magnifications.

Cancer center

In 1970, a small group of scientists at the Medical School formed a committee to explore an idea they had which would expedite cancer research in the Medical Center.

Their concept was a cancer center to coordinate and facilitate basic cancer research throughout the Medical Center.

Last month, this idea was fully realized with the dedication of the Centralized Facilities of the Center for Basic Cancer Research.

The Cancer Center was established to provide a focus for research, teaching and seminar programs. It is also responsible for defining which cancer-related areas need additional staff and then recruiting the necessary people.

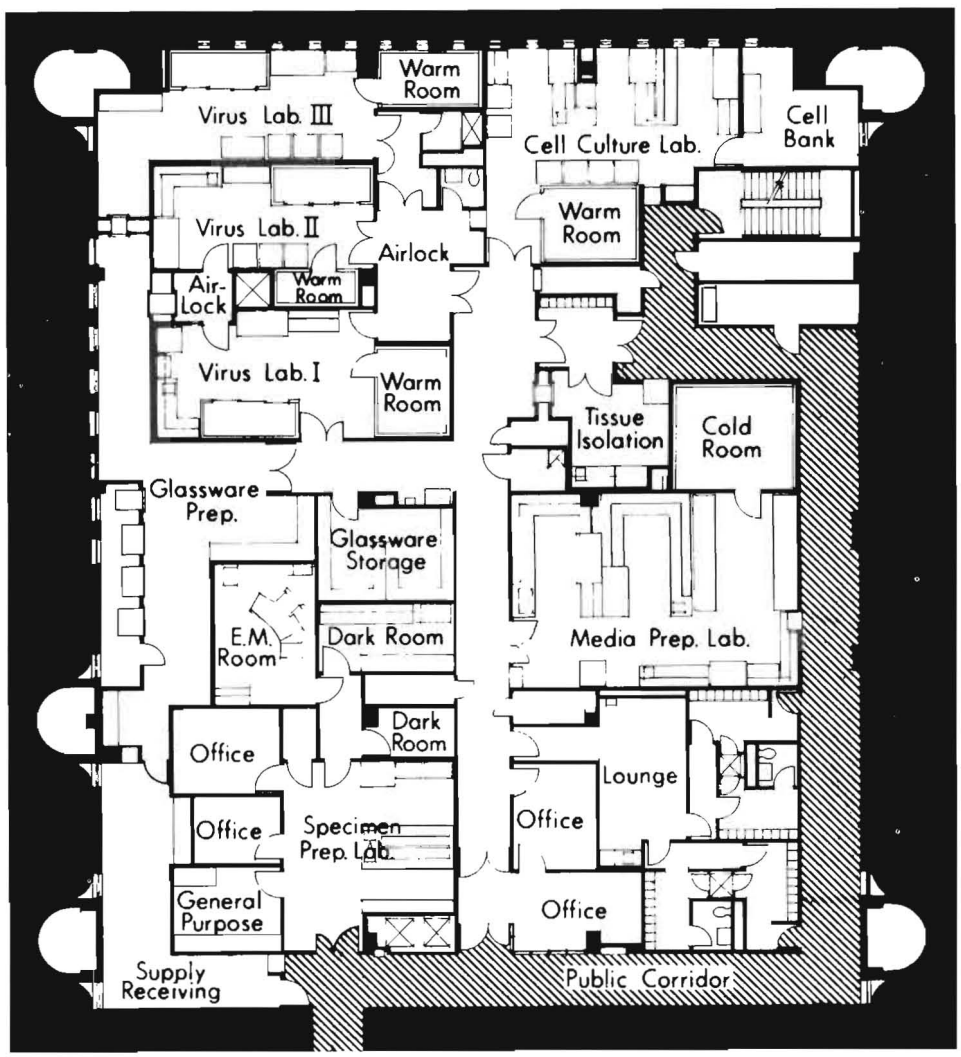
The Centralized Facilities were not completed until last year because the complex specialized center had to be planned and constructed.

These facilities, located in the McDonnell Medical Sciences Building, are the core of the Cancer Center and will provide services and supplies for cancer research laboratories throughout the Medical Center. Tissue Culture and Virus Production Laboratories will produce large amounts of tissue culture media, animal cells and viruses to be used by investigators in their own laboratories.

The Electron Microscopy Center will provide electron microscopy photography of viruses, cells and cell surfaces.

Fewer than ten such centers exist in the United States. A unique aspect of the facilities is that they will supply services to researchers regardless of departmental lines.

"The main advantage of having one facility is that the basic work such as media preparation and production of viruses and cells can be accomplished in large quantities and distributed to the researchers when and as they need them," explains Heschel Raskas, Ph.D., associate director of the center. "This saves the individual investigators time and money for equipment and supplies, and allows them to become more involved with the creative aspects of their research."



Robert E. Thach, Ph.D., director of the center, explains another advantage is the high level of expertise which can be achieved by centralizing these services.

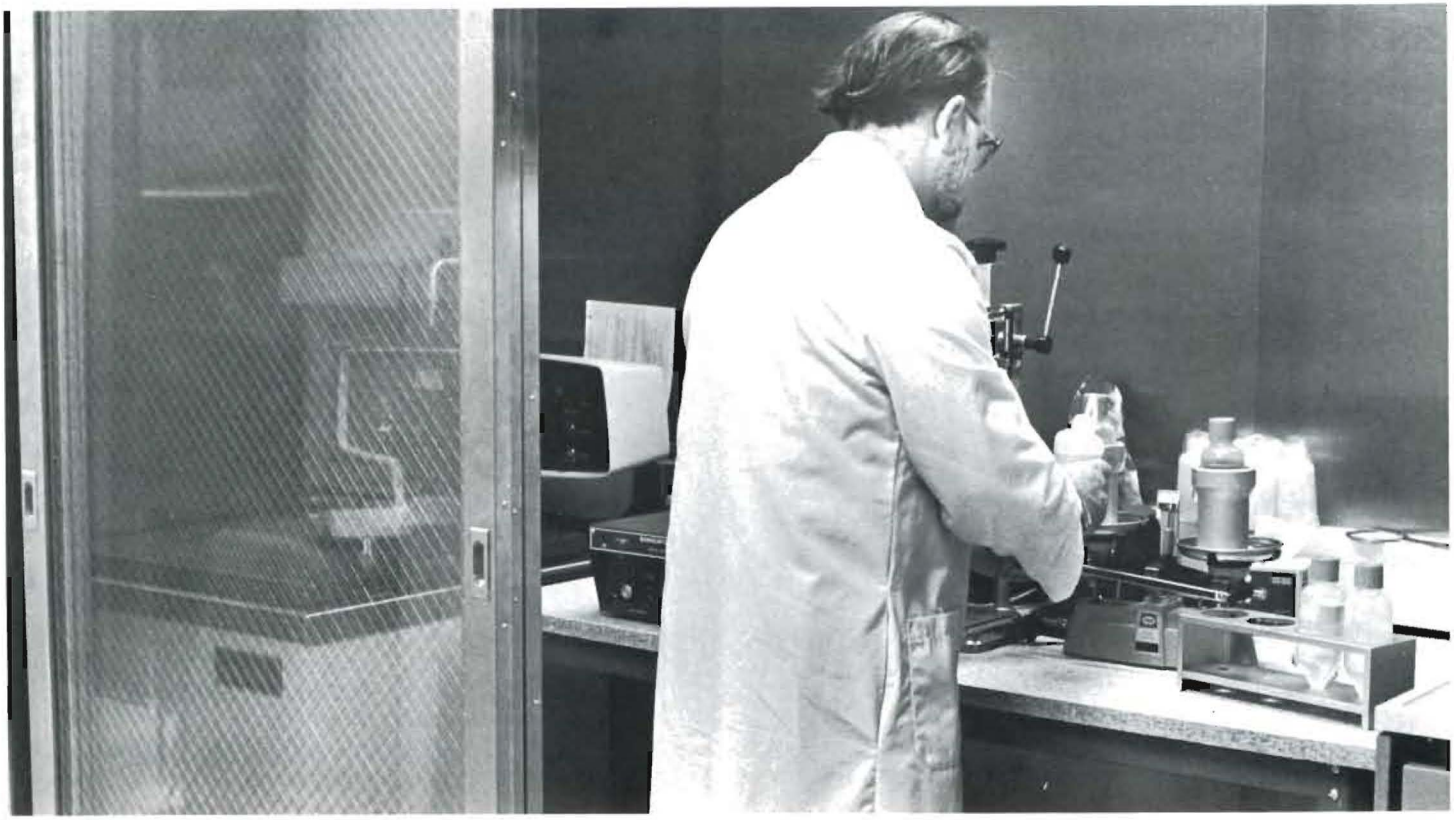
"Because it is a large facility which services many investigators, we can afford to have the most advanced technology available and an outstanding staff," he says.

"There's a level of expertise in the facility which few other laboratories could hope to achieve. The technology

Leonard Keay, Ph.D., director of the Tissue Culture and Virus Production Facility, and John Mulkie, virus and cell technician, examine a container of cells which produce virus.

Right: Darrell Dobbertin, assistant director of the Electron Microscopy Facility using the electron microscope.

Below: Keay in the virus lab's negative pressure hood.



would be impossible to duplicate," Thach says. "Some labs can do some of the things we do, but none can do all the things we're able to do."

More than 30 laboratories and 100 investigators utilize the services of the Central Facilities.

Construction of the Center was funded by a grant of more than $733,000 from the National Cancer Institute and a contribution of more than $254,000 from Washington University.

The Center is a biohazard facility which has been built to minimize the dangers involved with working with viruses. "The facilities are built so they are sealed off from the rest of the building," Thach says. "In addition, careful safeguards to protect people and the environment are followed."

Leonard Keay, Ph.D., director of the Tissue Culture and Virus Production Facility, says the facility has become well-known already. "We already have been asked by a manufacturing firm to evaluate some equipment which can produce cells on a large scale. We will use the machine for six months. Chances are we will be asked to make similar evaluations in the future." Thomas Rucinsky is director of the Electron Microscopy Facility.

Although construction was completed last year, the dedication program formalized the opening of the Central Facilities. Two guest speakers attended the program. Thomas J. King, M.D., director of the Division of Cancer Research Resources and Centers, National Cancer Institute, spoke on "Basic Research and the National Cancer Program." Howard M. Temin, Ph.D., McArdle Laboratory for Cancer Research at the University of Wisconsin and the 1975 recipient of the Nobel prize in medicine, also spoke on "RNA Viruses and Cancers."

Top: Heschel Raskas, Ph.D., associate director of the center, with Howard M. Temin, Ph.D., and Thomas J. King, M.D., speakers at the dedication program, and Robert E. Thach, Ph.D., director of the center.

Left: Pat Pruitt and Lovey McElroy prepare and label containers for cell media in the media preparation lab.

WUMS staff member travels 25,000 miles for United Nations

When an official in the Ministry of Education in Jakarta decides that elementary school children need to learn about population problems and family planning, he can turn to a United Nations-funded clearing house in Bangkok to find out how other countries have developed such curriculums.

If a union official in the Philippines decides large families of his union members are eroding the gains he negotiated in their pay scales, he can ask a U.N.-funded clearing house whether someone has devised a way to get this point across to adult workers in colloquial language.

If a village doctor in rural India finds side effects occurring frequently after insertion of IUDs, he can ask a clearing house in New Delhi for information. It not only will provide him with medical advice, but also help in explaining the problems to the village women, especially to the midwives with whom the women come in close contact.

These are only some of the services U.N.-funded clearing houses provide. Last autumn the U.N. Fund for Population Activities (UNFPA), sent a five-member mission to visit these clearing houses in the Pacific region.

The American on the team was Estelle Brodman, Ph.D., librarian at the School of Medicine and professor of medical history. The assignment lasted about eight weeks, during which she travelled some 25,000 miles.

The group was to determine how well the clearing houses were meeting the needs of the users in the area and whether other needs were developing which were not being met.

One of the questions facing them was the necessity for national, rather than regional or global, clearing houses. This issue is especially pertinent in countries where English is not

spoken, entailing translation of all materials before any could be used.

This is not the first time Brodman had worked in this geographic or subject area. In 1961-1962, she was visiting professor at Keio University in Tokyo. In 1968 she was expert consultant to what is now called the National Institute for Family Planning in New Delhi.

In 1970 Brodman performed the same task at the Regional Office of the World Health Organization in New Delhi. Three years later, with a group of other faculty from Asia and the West, she presented a three-week workshop in techniques for population documentation centers in Bangkok. In the U.S. she had been chairperson of a committee of the U.S. Agency for International Development which evaluated the work of the Technical Information System of the Carolina Population Council at the University of North Carolina.

"It has been interesting to see the changes in attitudes of individuals and governments on family planning over the years," she says. "Birth control is still a term which few governments wish to use, however, because of its implications of pressure in a very personal area of life. It may even connote genocide in some cases."

However, "most governments now have come to accept the fact that family planning and population dynamics must be integrated with other subjects to be acceptable to their citizens. That is why population is now taught as part of many subjects in schools." Brodman says in some places they teach how to figure percentages using examples from population data.

She says since most of the population of southeast Asian countries are illiterate, comic books, slide-tape presentations, posters and other non-readable media must be utilized. For example, the International Labor Office has produced a series of large blocks with pictures on them which can be used by a speaker to illustrate his talks.

Confusion can result, though, when countries exchange educational materials. A poster designed in southern Java showed men and women in native Indonesian dress; when it was used in Malaysia, problems arose because the clothing was so different they could not tell the man from the woman.

And the world-wide problem of putting scientific concepts in layman's language is complicated if the languages are different throughout the country, such as in India, where there are over 50 official languages. To overcome this problem, village officials, local school teachers and clergy are important "filtering devices." "That is why we tried to examine the position of national and local clearing houses in the scheme of things," Brodman says.

The mission found many problems with local and national clearing houses. Countries are at varying levels of sophistication in the use of any means of scientific transfer. Even libraries, Brodman says, which are taken for granted in developed countries, are new experiences for some countries.

"They don't know what such institutions can do for them, how they can use them or how much money it would take to run them. But it is a matter of national pride in many places to say the country has a national clearing house."

Profound changes are taking place in information processing, Brodman points out. "A global population information network is technically possible today, using computers and satellites, but it may be too expensive and perhaps too sophisticated for some countries to use such a system."

Many countries, she notes, do not even have the back-up equipment needed, such as photocopiers and microfilm reading machines.

Before departing, the group was briefed first at the U.N. in New York, then at UNESCO (United Nations Educational, Social and Cultural Organization) in Paris and finally at the WHO (World Health Organization) in Geneva. After the trip, the group reported in person to the UNFPA before returning home to write their reports.

Brodman says one of the human interest aspects of the trip was her observation of changes in the area as a result of the transformation of many governments into one-party systems. This had occurred recently in both India and Thailand. In fact, says Brodman, the change in government in Thailand happened shortly before the groups were scheduled to go to Bangkok. There was some question at that time whether it would be safe for the mission to visit that city.

"But everything seemed very quiet all the time we were there," she says. "There were curfews and soldiers in evidence everywhere, but for the most part the people were going about their regular business just as always.

"It was interesting to see the differences in the various non-democracies," she says. "In India, for example, there were large billboards and signs on all the buses with Mao-like injunctions, such as 'Talk less and work more,' or 'Be kind to visitors.' Newspaper ads pledged loyalty to the programs of Mrs. Gandhi, and there was little criticism of the government in the papers," Brodman says. Because India had had monsoons and several good years for crops, she says most people were better off than when she last visited the country.

One of the effects the non-democratic governments have on the clearing houses is the instability of the members of the government. "They are moved around from position to position, often before they have time to learn the problems in that position." She says such officials "often make decisions about clearing houses which might be the opposite of what their predecessors did. This results in wasted time and energy." The problem is wide-spread, she says, because in Asia all important institutions are parts of the governments.

Of all the cities she visited, two were especially important—Bangkok and New Delhi. Each had two clearing houses funded by the UNFPA, and each had to decide what their future courses would be. The fifth institution she visited, the Press Foundation of Asia, was in Manila. Brodman also con-

Helen Lewis-Jones (left), Program Officer for the U.N. Fund for Population Activities, consults with Estelle Brodman, Ph.D. Lewis-Jones came to St. Louis to collaborate with Brodman in compiling a final report.

sulted with officials in Pakistan and Indonesia.

In Bangkok, ESCAP (Economic and Social Council for Asia and the Pacific) has had a clearing house since 1971. "As the oldest and largest one," she says, "this clearing house has been asked to do a great many things, and unfortunately has tried to respond to all requests.

"It was tremendously successful at the beginning, but now they have spread themselves too thin," she says. "They're either going to have to stop some programs or get more people and money to carry them on. I'm inclined to think that the recent UNFPA decision to put more resources into national projects and fewer into regional and global projects will make it difficult for them to get the money that is needed for everything."

The other clearing house in Bangkok, UNESCO, has a more limited audience and an even more limited group of services, she says. Because of this, the center can delve into problems more deeply. The UNESCO clearing house has mobile teams which visit other Asian countries upon invitation from the governments. There they work with the local officials on their education problems and collect local "fugitive" or hard-to-locate literature for sending back to Bangkok.

The literature usually is items either mimeographed or typewritten, published in only a few copies for local use, but might contain data or statistics useful to other groups in other countries. Unless they are obtained quickly, Brodman says, it may not be possible to ever find a copy.

In New Delhi, she says, the mission found two different types of clearing houses. One at the National Institutes for Family Planning and the other at the regional Office of the World Health Organization.

Brodman says it was difficult to compare because the two had very different aims. The group felt, however, that the WHO had emphasized reviews of the literature rather than individualized services. "It also serves only the elitist medical groups in the area, with no one there to translate its findings into language understandable to policy makers and communication workers."

Almost all clearing houses publish newsletters, lists of new books and journal articles, translations and kits of "how to" materials. The centers also distribute publications to people working with and researching population problems.

Almost all of the clearing houses have networks of correspondents in cities throughout the region to alert them to important news.

"One of the most interesting ways that we saw of dispersing information about population and family planning is used by the Press Foundation of Asia in Manila. The Foundation utilizes free lance newspaper reporters ("stringers") throughout southeast Asia for stories on population. They collect the stories and furnish them to other newspapers, translated into local languages.

In this way, Brodman says, the Press Foundation hopes to replace the overwhelming abundance of stories in the papers about the "developed" world with articles on developing nations.

When asked for her view of the future of population clearing houses, she says, "the future course of population documentation centers and clearing houses is uncertain.

"On the one hand, computers and communication by satellite offer several possible global network roads. On the other hand, strengthening traditional libraries and knowledge resource bases might be the path for the next decade or so.

"Population itself, as now defined, may become so 'integrated' with other important social areas as to lose its singular identity. The present view," Brodman says, "is that population and family planning should be woven into the rest of life, rather than being considered a separate issue. It certainly is more effective when each aspect reinforces the others."

An example Brodman gives of this integration is lifestyle changes, such as urbanization of families without extended family groups and more women joining the labor force. "These changes, interwoven with population planning, are all mutually conducive to family planning."

One aspect that bothered her, she says, is that nobody seemed to be paying enough attention to the future of population documentation centers and clearing houses, not only in Asia, but also internationally.

"The changing definition of population, differing emphasis on population matters in many countries, the rise of nationalism everywhere and the new technology of communication all tend to foretell a change in the position of population documentation centers.

"What, for example, will be the relationship between national clearing houses and regional or global ones?" Brodman asks. "Who will take on the 'neutral' stance of the international group, whereby information is provided to countries who do not talk to each other directly, if regional clearing houses are dismantled? And who will provide the personalized services in their own language, which are now offered by national and local clearing houses if there are only regional and international ones?

"Finally," Brodman says, "who will care for population, narrowly considered, if only an umbrella-type clearing house for social affairs in developing countries remains?"

Brodman says these are the questions she would like to see addressed in the near future.

Why did the UNFPA select her for the mission? "Well, they needed someone who knew something about the area, who was a librarian, and who could go at the time that the mission was scheduled to leave. I guess I fitted those requirements," she says.

Brodman says this will probably be her last mission to the East, as future evaluations are likely to occur after her retirement. Her work in the transmission of scientific information will continue, however, but with a St. Louis base.

Etcetera

William H. Danforth, M.D., Chancellor of Washington University, and Mrs. Danforth read over the achievements of Washington and St. Louis Universities Medical Centers at the Tribute to St. Louis Medicine Dinner with Bernard A. Ehrenreich, executive director of the St. Louis chapter of the March of Dimes Foundation.

WUMS Honored During St. Louis Medicine Tribute

Oliver H. Lowry, M.D., Ph.D., professor of pharmacology and former head of the department, was honored for his contributions to the advancement of medical science last month during a week long Tribute to St. Louis Medicine.

Goronwy O. Broun Sr., M.D., dean emeritus and professor of medicine at St. Louis University also was recognized.

The St. Louis area chapter of The Birth Defects' March of Dimes Foundation sponsored the event to pay tribute to medicine in general, individual members of the profession and Washington and St. Louis Universities Medical Centers for their "tremendous accomplishments in improving the public health, particularly in the past 50 years."

Community leaders joined the March of Dimes to make the week a success. Broun and Lowry were recognized at a banquet which culminated the tribute.

Lowry was honored for his nationally recognized studies of the nervous system.

The recipient of many national awards and a member of the National Academy of Science, Lowry is world renowned for his work in microtechniques as well as for other research.

Dr. C. Rollins Hanlon, Chicago, pres-

ident of the American College of Surgeons was the principal speaker at the dinner.

Dr. Rollins spoke on "Medicine: Where We Are Going; Where We Have Been."

Howard M. Love, president of National Steel Corp., and chairman of the St. Louis Medicine Week said, "The achievements of medicine in every area of health care has been enormous, particularly in the past 50 years. We feel that the time is long past due to recognize these contributions.

"We want all deserving persons and institutions in medicine to know that we respect and appreciate what they have accomplished in furthering the public health and in contributing to the well-being of our fellow citizens through their scientific research, through treatment and devotion to the principles of their profession," he said.

The program paid particular tribute to the achievement of the medical schools of Washington and St. Louis Universities, local practitioners, scientific researchers and members of the nursing and related professions.

Names Make News

Carl Frieden, Ph.D., professor of biological chemistry at the School of Medicine, has received the 1976 St. Louis Section American Chemical Society Award.

The award is presented annually for outstanding contributions to chemistry. Frieden's particular area of research interest involves enzyme kinetics and the mechanism of enzyme action.

He is a graduate of Carleton College and of the University of Wisconsin, where he received his Ph.D.

Eli Robins, M.D., Wallace Renard Professor of Psychiatry, will receive the Paul H. Hoch award from the American Psychopathological Association on March 3. He will receive a gold medal and cash award at the Association's 67th annual meeting at the Hotel Americana in New York City.

Dr. Robins will receive the award for his lifetime research in the field of psychiatric illness, with a special emphasis on his clinical psychiatric research, and the diagnosis, treatment and classification of psychiatric illnesses.

Researchers Test Time-Release Contraceptive

A new time-release contraceptive which is injected into the cervix is being developed at the School of Medicine. However, unlike other contraceptive inoculations, this one should not affect the menstrual cycle nor prevent ovulation.

David W. Keller, M.D., assistant professor of obstetrics and gynecology, is researching the procedure which consists of injecting microscopic capsules beneath the surface of the cervix. The micro-capsules contain time-release doses of progesterone.

Progesterone, a female hormone, acts upon the cervical mucus, making it hostile to sperm penetration.

"We're not using a synthetic preparation," Keller stresses. "A woman's body naturally produces progesterone. In the middle of her cycle, protein fibers in the cervical mucus are optimally spaced for sperm passage. After ovulation progesterone is produced and the fibers intermesh. This position change makes it impossible for sperm to pass between the fibers and into the uterus."

Keller hopes to duplicate the natural progesterone production so the fibers will block sperm passage every day of the menstrual cycle.

He estimates the injections would be effective for about a year. The method is not designed for those who might soon change their minds about having a child, Keller says. However, he will be studying the possibilities of reversing the procedure. Work on the new contraceptive is funded by a grant from Northwestern University, Evanston, Ill.

Robert E. Sparks, Ph.D., professor of chemical engineering at Washington University, is assisting Keller. "Dr. Sparks is seeking to find a method of putting the hormone into the microcapsules so they will be time released," says Keller. "If they can be implanted once a year, it will be more convenient."

Keller and Sparks are testing the injections on cattle at the University of Missouri-Columbia. "We are studying in vitro sperm penetration," he explains. "We already can decrease sperm penetration significantly. We are planning to test the fertility of the animals and then develop reasonable release rates for the capsules.

"We hope to see its effectiveness in the next six months," Keller says. "We're just starting to measure the release rate of progesterone."

The contraceptive injections are advantageous because they should not interfere with the menstrual cycle. "This has a local effect only," Keller says. "There are no pain fibers in the cervix so it is a convenient place to do this type of injection. It is relatively painless."

Keller also foresees the possibility of utilizing an air gun such as those used by dentists, thus eliminating the need for a needle. The capsules would be shot directly into the cervix, being propelled by compressed air within the gun.

"It is not the answer to America's contraceptive problems, though," he says. "It is designed for people with relatively poor motivation, such as those who cannot remember to take a pill or who will not use other devices. This would be an alternative to sterilization, for someone who needs long-term contraception but who does not want to be sterilized."

Multiple Sclerosis Grant Received

The School of Medicine has received a three-year grant of $104,890 from the National Multiple Sclerosis Society to

continue support of research by Richard Bunge, M.D., professor of anatomy and neurobiology. Patrick Wood, Ph.D., research instructor, will collaborate with Bunge in this work.

Bunge is studying myelin-forming cells. In multiple sclerosis, for reasons not yet understood, the myelin sheath of the central nervous system nerve fibers is damaged and destroyed.

Bunge hopes to gain a better understanding of how the number of myelin-forming cells in the central nervous system is determined, how they are induced to form myelin sheaths, and to learn why the normal number of myelin-forming cells sometimes is not restored when the myelin sheath breaks down. In addition, he would like to better understand why supporting cells are able to reform myelin sheaths in certain demyelinating conditions and not in others.

This grant brings the Society's support of Bunge's research to $350,227 since 1960.

Students Honored For Scholastic Excellence

Twenty-four students at the School of Medicine were honored for scholastic excellence during the 1975-76 academic year at a December Awards Assembly.

Awardees from the St. Louis area and their honors are:

Michael R. Green—Carl F. and Gerty T. Cori Prize in Biochemistry, for superiority in the field;

Peter L. Jacobson—Lange Medical Publications Book Award for high academic standing during the junior year;

Thomas R. Kleyman—Lange Medical Publications Book Award for high academic standing during the sophomore year;

Keith L. Parker—Carl F. and Gerty T. Cori Prize in Biochemistry for superiority in the field;

Lee S. Portnoff—Lange Medical Publications Book Award for high academic standing during the sophomore year;

John J. Schier—Lange Medical Publications Book Award for high academic standing during the junior year;

Kenneth N. Scissors—Ciba Book Award for laudable extra-curricular community service.

Other students honored include:

Kendall H. Barker, Grosse Pointe Farms, Mich.—Dr. Robert Carter Medical School Prize, for meritorious performance during the freshman year;

George A. Chaitkin, Skokie, Ill.—Carl F. and Gerty T. Cori Prize in Biochemistry for superiority in the field;

Patrick N. Dwyer, Ruxton, Md.—Dr. Richard S. Brookings Medical School Prize for meritorious performance during the junior year;

Mitchell P. Fink, San Rafael, Calif.—a Medical Alumni Scholarship Fund Prize for scholastic excellence;

Erik M. Gregorie, Alexandria, Va.—Gill Prize in Anatomy for outstanding anatomical work;

Robert A. Gross, Worcester, Mass.—Edmund V. Cowdry Prize in Histology for outstanding performance in microscopic anatomy;

Bruce A. Kraemer, Tulsa, Okla.—Lange Medical Publications Book Award for high academic standing during the freshman year;

Joan K. Kreiss, Princeton, N.J.—Dr. Margaret G. Smith Award for outstanding achievement by a female student during the first two years of medical school;

Timothy J. Ley, Lakota, Iowa—Dr. Richard S. Brookings Medical School Prize for meritorious performance during the sophomore year;

Steven McGee, Portland, Ore.—Antoinette Frances Dames Prize in Physiology and Biophysics for scholastic superiority in the fields;

Ross E. Morgan, Wheat Ridge, Colo.—Dr. Robert Carter Medical School Prize for meritorious performance during the sophomore year;

Timothy Patton, Lacey, Wash.—Chouke Prize in Anatomy for superior scholarship in the field;

Victor L. Schuster, Glenwood, Iowa—Dr. Robert Carter Medical School Prize for meritorious academic performance;

James E. Schwob, Iowa City—Lange Medical Publications Book Award for high academic standing during the freshman year;

Allen J. Sedman, Southfield, Mich.—Antoinette Frances Dames Prize in Physiology and Biophysics for scholastic superiority in the fields;

Mark C. Udey, Ft. Atkinson, Wis.—Dr. Richard S. Brookings Medical School Prize for meritorious performance during the freshman year;

Stephen G. Young, Topeka, Kan.—McCordock Book Prize in Pathology for general excellence in the field.

Students Named To AOA

Twenty-one students at the School of Medicine have been elected to Alpha Omega Alpha by the faculty and the 135 seniors.

AOA is a national honorary society recognizing outstanding scholarship and leadership in medicine and related fields. It is considered the most prestigious honor society in medicine.

St. Louis area students elected to the society are: John W. Campbell, David D. Desper, Peter L. Jacobson and John J. Schier.

Other students elected include: Laird A. Bell, Overland Park, Kans.; James T. Brown, Springfield, Mo.; Charles Carrasco, Ogden, Utah; Patrick N. Dwyer, Ruxton, Md.; Mitchell P. Fink, San Rafael, Calif.; Pamela G. Freeman, Clarkston, Ga.; Glenn S. Gollobin, Teaneck, N.J.; Warner C. Greene, Mesa, Ariz.; Kay Miller, Mill Valley, Calif.; Duane L. Mitzel, Vallejo, Calif.; John W. Ogle, Denver, Colo.; Thomas E. Phillips, Manhattan, Kans.;

Victor L. Schuster, Glenwood, Ia.; James W. Steger, Prospect, Ky.; Howard G. Welgus, Flushing, N.Y.; Richard F. Williams, Mt. Vernon, Mo.; and Scott W. Younkin, Springfield, Ill.

Class Notes

'20s

Sol Londe, '27, St. Louis, is retiring from the practice of pediatrics. Dr. Londe is an associate professor of pediatrics and has been on staff at W.U. for more than 40 years.

'30s

James F. Nolan, '38, Los Angeles, was honored at a testimonial dinner given by the Alumni Association of California Hospital. A. N. Arnesen, '28, Henry Schwarz II, '41, Theodore A. Lynn, '38, Louis Hemplemann, Jr., '38, participated in the program.

Irving L. Berger, '39, Cleveland, is president-elect of the American Group Psychotherapy Association.

'40s

Gordon F. Moore, '40, Alton, Ill., was honored at a dinner by the citizens of Alton for his outstanding contributions to the community. The city dedicated a park in his honor which will be officially called the Gordon F. Moore Park.

Ewald W. Busse, '42, has been named the Associate Provost and Dean of Medical and Allied Health Education at Duke University Medical Center, Durham, N.C.

William L. Topp, '41, Seattle, was elected chief-of-staff of the Virginia Mason Hospital.

Edward J. Twin, '45, Kansas City, Mo., is the executive director of the New Truman Medical Center, Primary Teaching Hospital for UMKC. He also is a member of the Missouri State PSRO council.

Robert A. Huckstep, '48, has served 12 years on the school board of the Farmington RVII school district, and for three years as president of the Governor's Conference on Education.

'50s

Kenneth Huey, '55, Sun City, Ariz., has been elected chief of the medical staff at Boswell Memorial Hospital.

Eugene Nagel, '59, is now professor and chairman of the Department of Anesthesiology at Johns Hopkins University.

David L. Winter, '59, Washington, D.C., NASA Director for Life Sciences, was elected corresponding member of the International Astronautical Academy.

James H. Dunlevy, Jr., '51, Fairfield, Iowa, has finished one year as president of the Jefferson County Medical Society. He has served on the executive council of the Lutheran Church in America for the past seven years.

'60s

R. Michael Sly, '60, professor of pediatrics and director of Pediatric Allergy and Immunology at Louisiana State University Medical Center, New Orleans, has written a book entitled *Pediatric Allergy.*

Robert Waldman, '63, Morgantown, W.Va., has been named professor and chairman of West Virginia University's Department of Medicine.

Charlie W. Shaeffer, Jr., '64, Palm Springs, Calif., is the chief of cardiology at Eisenhower Medical Center, Palm Desert.

Elliott Prather Palmer, '66, recently has been appointed to the associate staff in the Department of Neurology at the Lahey Clinic in Boston. Dr. Palmer is a member of AMA and a junior member of the American Academy of Neurology.

Ronald E. Rosenthal, '61, Nashville, was recently awarded an NIH grant to continue "Studies of Synovial Response to Acute Trauma." He also was appointed to the Tennessee Chapter of the Committee on Trauma of the American College of Surgeons, and will continue as associate professor of orthopedics and rehabilitation, and associate professor of anatomy at Vanderbilt University.

Morris W. Pulliam, '66, was appointed assistant professor of neurological surgery, University of Missouri and chief of section of neurological surgery, Veterans Hospital, Columbia.

'70s

John D. Reinhard, '73, Chicago, was awarded the Norris L. Brookens Award from the Illinois Society of Internal Medicine. This award is given to the most outstanding resident in internal medicine in the state.

James Seegers, '73, received a MAP-Reader's Digest International Fellowship. Dr. Seegers is assigned to Monrovia, Liberia for three months. Made possible by a grant from the founder of *Reader's Digest,* DeWitt Wallace, the program provides three-month assignments to rural mission hospitals and clinics in remote parts of the Third World.

Lee A. Rigg, '71, La Jolla, Calif., has completed residency in OB/GYN and a post-doctoral fellowship in Reproductive Endocrinology.

Former House Staff and Former Faculty

Ian M. Smith, M.D., Johnson City, Tenn., has been appointed professor and chairman, Department of Internal Medicine at the new medical school, East Tennessee State University.

Heskel M. Haddad, M.D., is editor-in-chief of *Metabolic Ophthalmology,* a new international journal of basic research and clinical applications. The magazine is the official publication of the International Society on Metabolic Eye Disease.

Howard N. Ward, M.D., is the director of Medical Education, Stormont-Vail Hospital, Topeka, and assistant professor of medicine at the Kansas University Medical Center.

Leonard Wartofsky, M.D., Kensington, Md., has been appointed chief of the Kyle Metabolic Unit and Endocrine-Metabolic Service of the Walter Reed Army Medical Center.

J. Joseph Marr, M.D., is professor of medicine and microbiology and Director of the Division of Infectious Diseases at St. Louis University Medical School.

Health Care Administration

Stephen M. Patz, '69, has authored an article entitled "One Hospital's Approach to Word Processing" which was published in the October issue of *Medical Record News*. Patz is assistant administrator at Sinai Hospital of Detroit.

James A. Felts, assistant professor of anesthesiology at Washington University School of Medicine, was re-elected Speaker of the House of Delegates of the American Society of Anesthesiologists at the annual meeting which was held in San Francisco in October.

Washington University Medical Center Alumni Contributors—1976 Student Loan Fund

Over the years this Fund has assisted scores of Washington University medical students in meeting their expenses, especially those of an emergency nature. As educational costs continue to rise, the Fund assumes increasing importance. Grateful thanks is extended to all 1976 contributors.

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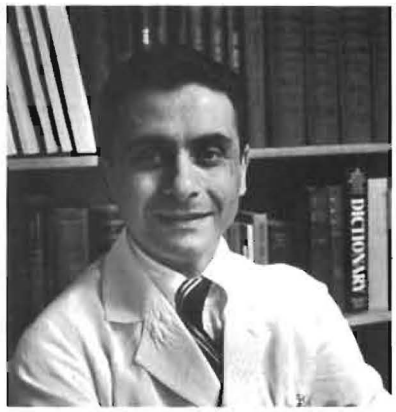
Continuing Medical Education Calendar

DATE	PROGRAM	CHAIRMAN
March 7-May 23	Internal Medicine Board Examination Review	Russell Eggebrecht, M.D. Richard Ratzen, M.D.
April 11-12	4th Annual Symposium on Obstetrics & Gynecology	George Wulff, M.D.
April 21-22	The Borderline Child	Doris Gilpin, M.D.
April 21-23	Eye Residents Seminar	Robert Feibel, M.D.
April 22	An Approach to the Patient With Diarrhea	Gary Zuckerman, D.O.
May 5-7	Jewish Hospital Medical & Surgical Program	Jerry Meyers, M.D.
May 11-13	Washington U. Med. Center Alumni Reunion	Robert Karsh, M.D. Edward Lansche, M.D. Robert Packman, M.D. Edward Reinhard, M.D.
May 18	Surgical Problems in Children	Martin Bell, M.D.
May 20-21	Neuromuscular Diseases	Michael Brooke, M.D.
May 26-27	Current Topics in Hypertension & Its Management	H. Mitchell Perry, Jr., M.D.
June 9	Perinatal Medicine	Richard Marshall, M.D.



Vice Chancellor Comments:

"To be worthy to serve the suffering" is the motto of Alpha Omega Alpha, the medical honor society. The motto expresses beautifully the high ideals of our profession. It recognizes that it is a privilege to be a physician—a privilege, much sought after and widely respected, that must be justified throughout one's professional life.

Physicians justify their privileges by adhering to a code of honor that governs their dealings with the sick and injured and with one another. No profession can hope to enjoy society's trust without such a code that *truly* guides and and fortifies its practitioners.

At different times and in various places, such codes for physicians have been expressed differently, but they always demand commitment—through self-discipline, hard work, and personal sacrifice—to medicine's high ideal of devotion to the suffering. Further, physicians are expected never to forget their debt to society for having educated and trained them and their debt to patients who allowed them to participate in their care and so learn to be physicians. Honor obligates us to acknowledge our debts to those who made our privileges possible and requires us to repay in kind the sacrifices of others made in our behalf.

Great professional privilege—such as that enjoyed by physicians—can only be countenanced when coupled to a demanding code of responsibility and obligation to which the profession gladly adheres. Such codes, like our bodies, become flabby when not subjected to regular exercise and challenge. They are then easily compromised or even dismissed cynically when confronted by economic, social, and political "realities." But we must never misunderstand: our privileges are inseparably linked to our obligations. If the latter become "unrealistic" or "outmoded," the former will surely disappear.

Samuel B. Guze, M.D.
Vice Chancellor for Medical Affairs

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